

OCULAR CYCLOSPORINE COMPOSITION

This is a continuation of U.S. Ser. No. 07/187,823 filed Apr. 29, 1988, now abandoned, which is a continuation-in-part of U.S. Ser. No. 092,466 entitled "Method of Increasing Tear Production by Topical Administration of Cyclosporin" filed Sep. 3, 1987, now U.S. Pat. No. 4,839,342, issued Jun. 13, 1989 by Renee Kaswan and U.S. Ser. No. 117,218 entitled "Method of Treating a Specific Antigen Mediated Immune Response by Local Administration of Cyclosporin" filed Nov. 4, 1987 by Renee Kaswan, now abandoned.

BACKGROUND OF THE INVENTION

Cyclosporine is a metabolite isolated from the culture broths of the fungal species *Tolypocladium inflatum* Gams. A neutral, hydrophobic cyclic peptide composed of eleven amino acid residues, cyclosporine includes a previously unknown N-methylated amino acid composed of nine carbon atoms. A number of additional cyclosporines (B, C, D, E, and G) have been reported since the first cyclosporine was isolated (CsA). As described in U.S. Pat. No. 4,117,118 issued Sep. 26, 1978 to Harriet al, cyclosporine is readily soluble in most of the usual organic solvents and practically insoluble in petroleum ether and water. As distributed by Sandoz Ltd, Basel, Switzerland, under the tradename Sandimmune, cyclosporine for oral administration is dissolved in olive oil for further dilution with food and in polyoxyethylated castor oil and ethanol for intravenous injection.

Cyclosporine is a potent immunosuppressive agent used to prolong survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine and lung. The exact mechanism of action is not known but experimental evidence suggests that the effectiveness of cyclosporine is due to specific and reversible inhibition of immunocompetent cells, primarily T-helper cells. Lymphokine production, gamma interferon production and release of interleukin-2 or T-cell growth factor are also inhibited by cyclosporine.

Cyclosporine is primarily administered orally or by injection. Unfortunately, parenteral administration of the drug has been associated with renal toxicity, hepatotoxicity, and increased incidence of opportunistic infection. The quantity of drug required for systemic administration is also prohibitively expensive.

As described in U.S. Pat. No. 4,649,047 issued Mar. 10, 1987 to Kaswan, topical administration of cyclosporine is useful in the treatment of a variety of immune mediated disorders of the eye, including uveitis and phacoanaphylactic endophthalmitis. This is also the preferred mode of administration to avoid the undesirable side effects and cost of systemic administration.

As described in U.S. Ser. No. 092,466 now U.S. Pat. No. 4,839,342 (Jun. 13, 1989) entitled "Method of Increasing Tear Production by Topical Administration of Cyclosporin" filed Sep. 3, 1987 by Renee Kaswan, cyclosporine has now been discovered to have additional mechanisms of action which can be used to enhance or restore glandular function, as demonstrated by significant increases in tear production in the eyes of both normal and diseased animals. Although it is not clear at this time how the cyclosporine is achieving this effect, the mechanism of action appears to be independent of the immunosuppressant mechanism.

Although cyclosporine has been topically administered in a variety of vehicles including arachis oil, a commercially available ointment base, and castor oil, the conventional carrier is olive oil. Unfortunately, topical administration of cyclosporine in olive oil to the eye of either humans or dogs is frequently accompanied by a burning sensation, pain, and redness. In some cases, other side effects have been observed including lid edema and periocular alopecia (hair loss around the eye). Similar problems have occurred with topical ophthalmic use of cyclosporine in the other vehicles. Studies have now demonstrated that these unpleasant side effects are due to the carrier, not to the cyclosporine. Unfortunately, cyclosporine is of very limited solubility and the number of acceptable carriers for ophthalmic use is limited.

It is therefore an object of the present invention to provide a composition containing an effective concentration of cyclosporine for topical ophthalmic use which does not cause burning, redness or irritation.

It is a further object of the present invention to provide a composition for topical ophthalmic use which is stable upon storage.

It is another object of the present invention to provide a composition for topical ophthalmic use which promotes normal healing of the epithelial surface of the eye.

SUMMARY OF THE INVENTION

Cyclosporine compositions for topical ophthalmic use for treatment of immune disorders, to enhance or restore tear production, and to enhance or effect normal healing of the surface of the eye, consisting of cyclosporine dissolved in corn oil. The composition may further include antioxidants, lubricants, antibiotics, antifungals, antivirals, pilocarpine, vasoconstrictors, surfactants, wetting agents, anti-inflammatory agents (i.e. corticosteroids), preservatives, mucolytic agents (i.e. bromhexine, acetylcysteine), as well as other compounds.

The preferred composition is 2% cyclosporine, 1 mole % alpha tocopherol and 0.005% methyl paraben in corn oil.

Despite the apparent similarities in chemical structure, studies demonstrate the significant difference in comfort and incidence of side effects between cyclosporine in previously described carriers such as olive oil and cyclosporine in corn oil, both with and without preservative and antioxidant. These studies also establish that topically applied cyclosporine can be used to promote or effect normal healing and prevent or reverse scar formation on the ocular surface.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph demonstrating the effect of topical cyclosporine on lacrimation (STT mm/min) over time (days) in twelve normal male beagle dogs; following three days of baseline measurement with no treatment, six dogs were treated with 2% cyclosporin in olive oil. applied topically two times daily, and six dogs were treated with placebo (olive oil) applied topically two times daily. The STT were determined twice daily in the cyclosporin treated dogs (—) and in the olive oil treated dogs (—). Following 7 days all dogs were crossed over into the opposite treatment groups for an additional three days.

FIG. 2 is a comparison of the appearance of the eye of a dog suffering from keratoconjunctivitis sicca before